UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,376	10/14/2005	Mitsuyuki Shimada	RCK-36	5717

35969 7590 08/09/2007

JEFFREY M. GREENMAN
BAYER PHARMACEUTICALS CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516

EXAMINER	
LEESER, ERICH A	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,376	SHIMADA ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1 and 3-13* is/are allowed.

6)☒ Claim(s) *2 and 14-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-10-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-26 are pending and under examination.

Priority

Acknowledgment is made that this application is a 371 of PCT/EP03/10377, filed September 18, 2003 and claims benefit of foreign application EPO 02021861.6, filed on September 30, 2002.

Information Disclosure Statement

The references cited in the IDS, dated March 10, 2005, are made of record.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18-22 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 and 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, in claim R^{201} is unclear because on page 221 one definition is listed whereas on page 222 a different definition is provided. Clarification is required.

Claims 18-22 provide for the use of the fused azolepyrimidine derivative for the treatment of various diseases and conditions, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to treat inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy using a compound of formula (I) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention/ The breadth of the claims:

The instant invention is drawn to derivative compounds, medicaments, processes and methods to treat inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy using a compound of formula (I).

The state of the prior art:

The prior art at the time the invention was made clearly shows that the scientific community was unsure of the therapeutic value of using PI3Kγ inhibitors to treat arthritis and rental failure: "Treatment reduced glomerulonephritis and prolonged lifespan, suggesting that P13Kγ *may* be useful in the treatment of chronic inflammation." (Emphasis added). Barber, et al., *PI3Kγ Inhibition Blocks Glomerulonephritis and Extends Lifespan in a Mouse Model of Systemic Lupus*, Nature Medicine, Vol. 11, No. 9, 933-935 (2005). The same was the case with

regards to the treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and ischemia: "These results suggest that D2 dopaminergic receptor activation plays an important role in neuroprotection against glutamate cytotoxicity and that the up-regulation of Bcl-2 expression via the PI3K cascade is, *at least partially*, involved in this effect." (Emphasis added). Kihara, et al., *Protective Effect of Dopamine D2 Agonists in Cortical Neurons Via the Phosphatidylinositol 3 Kinase Cascade*, Journal of Neuroscience Research, 70, 274-282 (2002).

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of formula (I) would be useful to treat inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy.

Amount of guidance/working examples:

There are no examples in the specification showing that the instant compounds can be used to treat inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial

contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy using a compound of formula (I). Although the "Solid-Phase Lipid Kinase Assay" on page 40 and the "Chemotaxis assay" on page 46 appear to show activity of P13Kγ inhibitors, this evidence does not definitively prove that the compounds of formula (I) are capable of treating inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy.

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient to treat inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy using a compound of formula (I), one of ordinary skill in the art, even with a high level of skill, is unable to practice the invention as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds

exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to make and use Applicant's invention to treat inflammatory or immunoregulatory disorders, asthma, rhinitis, allergic diseases, autoimmune pathologies, rheumatoid arthritis, Grave's disease, atherosclerosis, neurodegenerative disorders, Alzheimer's disease, focal ischemia, diabetes, cancer, myocardial contractility disorders, heart failure, ischemia, pulmonary hypertension, renal failure or cardiac hypertrophy using a compound of formula (I) without undue experimentation.

Allowable Subject Matter

Claims 1 and 3-13 are patentable over Jacobson, et al., U.S. Patent No. 6,066,642. The reference teaches dihydropyrimidine compounds similar to the compounds of the instant application except the compounds of the reference teach furanyl in the R^4 position and in the corresponding position in the application, R^4 is limited to hydrogen or C_{1-6}alkyl. Therefore, the claims appear to be free of the prior art of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Erich A. Leeser
Patent Examiner, Art Unit 1624
United States Patent and Trademark Office
400 Dulany Street, Remsen 5C11
Alexandria, VA 22314-5774
Tel. No.: (571) 272-9932

James O. Wilson
Supervisory Primary Examiner, Art Unit 1624
United States Patent and Trademark Office
400 Dulany Street, Remsen 5A11
Alexandria, VA 22314-5774
Tel. No.: (571) 272-0661